Seizure control as a new metric in assessing efficacy of tumor treatment in low-grade glioma trials

Avila, E K ; Chamberlain, M ; Schiff, D ; Reijneveld, J C ; Armstrong, T S ; Ruda, R ; Wen, P Y ; Weller, M ; Koekkoek, J A F ; Mittal, S ; Arakawa, Y ; Choucair, A ; Gonzalez-Martinez, J ; MacDonald, D R ; Nishikawa, R ; Shah, A ; Vecht, C J ; Warren, P ; van den Bent, M J ; DeAngelis, L M

Abstract: Patients with low-grade glioma frequently have brain tumor-related epilepsy, which is more common than in patients with high-grade glioma. Treatment for tumor-associated epilepsy usually comprises a combination of surgery, anti-epileptic drugs (AEDs), chemotherapy, and radiotherapy. Response to tumor-directed treatment is measured primarily by overall survival and progression-free survival. However, seizure frequency has been observed to respond to tumor-directed treatment with chemotherapy or radiotherapy. A review of the current literature regarding seizure assessment for low-grade glioma patients reveals a heterogeneous manner in which seizure response has been reported. There is a need for a systematic approach to seizure assessment and its influence on health-related quality-of-life outcomes in patients enrolled in low-grade glioma therapeutic trials. In view of the need to have an adjunctive metric of tumor response in these patients, a method of seizure assessment as a metric in brain tumor treatment trials is proposed.

DOI: https://doi.org/10.1093/neuonc/now190

Seizure Control as a New Metric in Assessing Efficacy of Tumor Treatment in Low-Grade Glioma Trials

Edward K. Avila[1] , Marc Chamberlain[2], David Schiff[3], Jaap C. Reijneveld[4], Terri S. Armstrong[5], Roberta Ruda[6], Patrick Y. Wen[7], Michael Weller[8], Johan A.F. Koekkoek[9], Sandeep Mittal[10], Yoshiki Arakawa[11], Ali Choucair[12], Jorge Gonzalez-Martinez[13], David R. MacDonald[14], Ryo Nishikawa[15], Aashit Shah[16], Charles J. Vecht[17], Paula Warren[18], Martin J. van den Bent[19], Lisa M. DeAngelis[1]

[1]Department of Neurology, Memorial Sloan Kettering Cancer Center, New York 10065 (EA LMD); [2]Department of Neurology, University of Washington, Seattle, WA 98104 (MC); [3]Department of Neurology, University of Virginia, Charlottesville, Va.22903 (DS); [4]Department of Neurology, Vumc Cancer Center, The Netherlans (JCR); [5]Department of Family Health, University of Texas Health Science Center, Houston, Texas (TSA); [6]Department of Neuro-Oncology, City of Health and Science Hospital, Torino, Italy(RR); [7]Center for Neuro-Oncology, Dana-Farber Cancer Institute/ Brigham and Women's Center, Boston, MA. 02215 (PW); [8]Department of Neurology, University Hospital Zurich, Zurich, Switzerland (MW); [9]Department of Neurology, Leiden University Medical Center, The Hague, The Netherlands (JAFK); [10]Department of Neurosurgery, Wayne State University, Detroit, Michigan (SM); [11]Department of Neurosurgery, Kyoto University School of Graduate Medicine, Kyoto, Japan (YA): [12]Department of Neurology, Southern Illinois University School of Medicine, Springfield, Illinois (AC); [13] Department of Epilepsy and Surgery Center, Cleveland Clinic, Cleveland, Ohio (JGM); [14]Department of Neurology, London Health Sciences Center, London, Ontario, Canada (DRM); [15]Department of Neurosurgery, Saitama Medical University, Saitama, Japan (RN); [16]Department of Neurology, Wayne State University School of Medicine, Detroit, Michigan (AS); [17] Service Neurologie Mazarin, CHU Pitie-Salpetriere, Paris, France (CJV); [18]Department of Neurology,The University of Alabama, Birmingham, Alabama (PW); [19]Department of Neuro-Oncology, Brain Tumor Center, Erasmus MC Cancer Institute, Rotterdam, The Netherlands (MJB)

Corresponding author: Edward K. Avila, DO

Department of Neurology

Memorial Sloan Kettering Cancer Center

1275 York Avenue

New York, NY 10065

Phone #: (212) 639–3718

Fax #: (646) 422–2174

Email: avilae@mskcc.org

Total text word Count: 6,152 (including references and figure legend)

Funding: This research was funded through the NIH/NCI Cancer Center Support Grant P30 CA008748

Conflict of interest for each author:

Edward K. Avila has no conflict of interest

Marc Chamberlain has no conflict of interest

David Schiff has no conflict of interest

Jaap C. Reijneveld has no conflict of interest

Terri S. Armstrong has no conflict of interest

Roberta Ruda has no conlict of interest

Patrick Y. Wen has no conflict of interest

Michael Weller has no conflict of interest

Johan A.F. Koekkoek has no conflict of interest

Sandeep Mittal has no conflict of interest

Yoshiki Arakawa has no conflict of interest

Ali Choucair has no conflict of interest

Jorge Gonzalez-Martinez has no conflict

David R. MacDonald has no conflict of interest

Ryo Nishikawa has no conflict of interest

Aashit Shah has no conflict of interest

Charles J. Vecht has no conflict of interest

Paula Warren has no conflict of interest

Martin J. van den Bent has no conflict of interest

Lisa M. DeAngelis has no conflict of interest

Abstract

Patients with low-grade glioma frequently have brain tumor-related epilepsy, which is more common than in patients with high-grade glioma. Treatment for tumor-associated epilepsy usually comprises a combination of surgery, antiepileptic drugs (AEDs), chemotherapy and radiotherapy. Response to tumor-directed treatment is measured primarily by overall survival and progression-free survival. However, seizure frequency has been observed to respond to tumor-directed treatment with chemotherapy or radiotherapy. A review of the current literature regarding seizure assessment for low-grade glioma patients reveals a heterogeneous manner in which seizure response has been reported. There is a need for a systematic approach to seizure assessment and its influence on health-related quality-of-life outcomes in patients enrolled in low-grade glioma therapeutic trials. In view of the need to have an adjunctive metric of tumor response in these patients, a method of seizure assessment as a metric in brain tumor treatment trials is proposed.

Key words: Seizures, metric, low-grade, glioma, scale

Importance of the Study: This position paper will describe the importance of developing a metric to assess seizure frequency in brain tumor treatment trials. Seizure frequency can affect many aspects of a patient's life including vocation and the ability to drive. Seizure control can be achieved through treatment of low-grade glioma and is seen after gross total resection, chemotherapy or radiotherapy. As such, seizures can be a surrogate marker for treatment response in patients with low-grade glioma and may serve as an important secondary endpoint. The current paper will propose a new method in which seizure assessment can occur in low-grade glioma treatment trials.

Introduction

Adults with low-grade glioma (LGG: World Health Organization [WHO] grade I and II gliomas) have a more favorable prognosis than those with higher grade gliomas (WHO grade III and IV), but ultimately most die of their disease. Current optimal treatment of adult WHO grade II gliomas results in a median overall survival (OS) of 7 years, (range 5-14 years), making health-related quality of life (HRQOL) an important outcome in this population of typically young adults.[1] Seizures are reported in up to 60-80% of LGGs (WHO grade II gliomas) and 50-60% of WHO grade III anaplastic gliomas. Moreover, recent studies have suggested a higher seizure frequency at onset in gliomas expressing the isocitrate dehydrogenase (IDH) mutation findings seen in 70% of low-grade gliomas.[2] HRQOL is highly affected by seizures and antiepileptic drugs (AEDs), and epilepsy can cause significant disability in patients with LGG. Progression-free survival (PFS) and OS are the usual metrics of anti-tumor therapies; however, surrogate and clinically relevant determinants of outcome such as seizure control are pertinent in LGG.[3]

Localization-related epilepsy, as defined by the International League against Epilepsy (ILAE), causes unprovoked seizures from a discrete area of epileptogenic brain.[4] This is the type of epilepsy which arises in patients with LGG where the epileptic focus usually originates from brain immediately surrounding the tumor, the so-called peri-tumoral brain region.[5] However, the epileptic zone often includes regions well beyond the visible tumor margin.[6] The unpredictability of epilepsy affects the patient's psychological and functional well-being, and can compromise numerous activities of daily living including but not limited to driving, working with machinery, and swimming. A patient's HRQOL is particularly affected when seizures are uncontrolled, which occurs in up to 30% of patients with brain tumor-related epilepsy (BTRE).[7] In addition, AEDs can have a negative effect on self-reported HRQOL measures, particularly in those on polypharmacy or those on AEDs for greater than 6 months.[8] Furthermore, AEDs may be a significant cause of impaired cognition in LGG patients which can often have a greater adverse impact than the underlying tumor or prior cranial radiotherapy (RT).[9] Taken together, these data suggest that both seizures and their treatment can significantly compromise HRQOL.[10]

The importance of measuring seizure control in brain tumor trials

Control of seizures has a direct relationship to HRQOL, driving, vocation, sexual activity, and mood.[11-13] Patients whose seizures are well controlled also have lower morbidity and mortality, such as sudden unexpected death in epilepsy (SUDEP) compared to patients with uncontrolled epilepsy (incidence of 1/1,000 in poorly controlled versus 1/150 in well controlled).[14,15] Seizure control is the primary endpoint in trials examining novel therapeutics in epilepsy. Why then should it be an endpoint in assessing brain tumor therapies? Uncontrolled seizures have a major impact on a patient's function. Brain tumor treatments are assessed by their direct effect on survival and the disease itself as measured by neuroimaging, but radiographic regression in LGG is typically slow and often difficult to measure. In contrast, seizure frequency is quantifiable and may serve as a surrogate marker of tumor response although this is still being investigated.[16] Inadequate seizure control, even without radiographic evidence of tumor progression, has been used as a reason to initiate further treatment of a LGG and loss of seizure control can be an early indicator of tumor progression.[17] Likewise, restoration of seizure control may be the first indicator that a therapy is effective.[16,17] In addition, for patients with poorly controlled seizures, the majority of whom have normal or non-progressive neurologic exams, seizure control is often the only clinical parameter that is clinically relevant. Thus, it is important to consider seizure control when assessing a new tumor-directed therapy – not to replace the standard measures of tumor response (PFS and OS) but to quantify clinical outcomes, to potentially identify an early signal of anti-glioma efficacy, and to establish quality of survival. This could be particularly relevant when investigating novel compounds that target common pathways of epileptogenesis and tumor cell proliferation such as the use of rapamycin in tuberous sclerosis complex.[18,19] Thus, it is important to standardize the methods used for such a determinant in patients with LGG and epilepsy. The following review will outline seizure outcomes after tumor-directed treatments and the manner in which seizure outcome is determined in epilepsy trials. The RANO (Response Assessment in Neuro-Oncology) seizure working group then proposes how this methodology can be implemented in LGG trials.

Seizure outcome after surgery

Maximal glioma resection has been repeatedly shown to improve seizure control. Whether the lesion is temporal or extra-temporal, an Engel class I (free of disabling seizures) is achieved in 80% of patients with maximal resection (Table 1).[20,21] The manner in which a glioma is surgically treated differs from a resection performed specifically for non-tumor related epilepsy in which direct cortical recording or electrocorticography (ECoG) or extra-operative invasive methods are often used. These intraoperative techniques are not usually implemented during glioma surgery and may not be relevant for improving seizure outcomes in brain tumor patients, specifically when the BTRE syndrome is less than one year duration.[22] However, utilization of an epilepsy surgery approach with extra-operative invasive recording for patients with BTRE can help to localize the epileptogenic zone, provide insight into pathophysiology of BTRE, and may lead to improved seizure-free outcomes.[6] For WHO grade I temporal lobe tumors such as dysembryoplastic neuroepithelial tumor (DNET) or ganglioglioma, temporal lobectomy with hippocampectomy leads to a more favorable seizure outcome compared with excision of the lesion alone.[23] However, complete tumor removal with or without hippocampectomy is rarely an option for the more common diffuse WHO grade II LGGs. Rarely, seizures can appear or intensify after tumor resection.

Seizure outcome after radiotherapy

There have been several studies examining the response of seizures in LGG patients treated with RT. RT for LGG (age>40 years or incomplete resection) prolongs PFS but not OS if administered at initial diagnosis versus at progression.[24] Seizure control has been evaluated as a secondary endpoint in RT trials including trials of brachytherapy, stereotactic radiosurgery and involved-field fractionated irradiation.[24-28] These studies examined many aspects of seizure response including seizure freedom, percentage of decrease compared to baseline seizure frequency, and improved Engel class.[10] In a large trial of RT (group 1, early treatment, group 2, late treatment) seizure freedom at 12 months was reported in 75% of those with early RT and 59% of those treated with delayed RT given at the time of progression.[24] In a

trial evaluating 30 patients with insular gliomas who received RT, Engel class I outcome was achieved in 70% with only 3% at Engel class III after therapy.[29] A large trial using fractionated stereotactic radiosurgery in 143 patients with LGG found a decrease in generalized seizures from 36% to 7% and a decrease in focal seizures from 34% to 17% six weeks after RT.[30] However, it is important to note in this study the role of AEDs was rarely reported or considered, therefore ignoring the contribution of AEDs to seizure control. A recent study analyzed the seizure outcome following conformal RT in a cohort of 43 patients with grade II and III glioma and medically intractable epilepsy in whom AED treatment was recorded and not changed during the study period. A reduction of seizure frequency ≥ 50% was obtained in 72% and 76% at 3 and 6 month after RT, respectively, while seizure freedom was achieved at 12 months in 32% of patients [25]

Seizure outcome after chemotherapy

Recent studies strongly suggest a correlation between improved seizure control and benefit from chemotherapy for LGG. There are no randomized controlled trials examining this relationship, but there are several prospective as well as retrospective studies.[10,31-35] The common theme has been that chemotherapy alone reduces seizure frequency irrespective of whether tumor response is measurable by neuroimaging. Seizure control is observed regardless of the chemotherapy regimen (e.g. temozolomide or a nitrosourea-based therapy such as PCV [procarbazine, lomustine, and vincristine]).[10] In a retrospective study of 66 patients with LGG who received temozolomide, 44% had improvement in seizure frequency with 41% achieving seizure freedom after 6 months.[36] A small prospective trial of 10 patients with unresectable LGG treated with neoadjuvant temozolomide showed a seizure reduction of 90% with one-half of patients achieving seizure freedom at an undefined follow-up period.[37] A separate prospective study evaluated the response of seizures to temozolomide at 3 month periods during treatment; a 50% reduction in seizure frequency was reported in 48% of patients with 13% achieving seizure freedom at the end of the study.[33]

Seizure classification

The ILAE has proposed several systems of classifying seizures and epilepsy syndromes since 1960. The ILAE published an update on seizure classification in 1981 and on epilepsy syndromes in 1989. More recently, new changes were suggested to reflect a more clinically based approach with inclusion of etiology;[38] however, for the purposes of brain tumor trials, seizure semiology can be best classified using the 1989 system. Seizures that arise from a brain tumor are all termed symptomatic, i.e. secondary to the underlying glioma.[4] In addition, seizures can be classified as focal epilepsy with or without secondary generalization. Seizures without secondary generalization can then be classified as either a simple partial seizure that manifests as motor, sensory, and/or visual abnormalities without alteration of consciousness, or as complex partial seizures that manifest as motor, sensory, and/or visual disturbances with alteration of consciousness. In addition, all generalized seizures that arise in a brain tumor patient are partial in onset whether clinically evident or not. Thus, even patients with a generalized tonic-clonic seizure at presentation likely have a focal onset and can be classified as secondarily generalized tonic-clonic or focal seizures evolving to a bilateral, convulsive seizure. The remainder of the ILAE classification system is not relevant in assessing seizures in brain tumor patients.

The National Institute of Neurological Disorders and Stroke (NINDS) developed a seizure classification tool that is often used for AED trials. Using this instrument, seizures are divided into generalized, focal or unclassified seizure type. Each seizure type may have associated stereotypic movements such as myoclonic jerks, atonic movements, with or without loss of consciousness (Table 2).[38,39] In the brain tumor population, dividing seizures into secondarily generalized or focal (partial) would likely be most pragmatic. Further stratification of seizures may make any assessment tool too cumbersome for routine use in brain tumor treatment trials where non-neurologists will play an important role in seizure assessment.

Data collection approaches for seizures

Counting seizures

Enumerating seizure frequency largely depends on patient reports. In epilepsy drug trials, patients are provided with seizure diaries, which provide a log of seizure frequency permitting an assessment of seizures over a standardized period of time. A seizure diary may be challenging for some patients with BTRE, either because of cognitive deficits or behavioral problems. Some patients, such as those with significant aphasia or amnesia, may require a care provider to report seizure frequency. Reliability is also a concern as recall bias may affect the actual number of reported seizures. However, studies correlating patient and observer recall of seizures show a good concordance; up to 81% in patients without brain tumors.[40,41]

Counting seizures can be challenging but the investigator can report seizure frequency in one of two ways: 1) the exact number of seizures, or 2) a relative change in frequency (few, many, fewer, or more seizures) compared to baseline.[42] The data can also be reported as a percentage change from baseline frequency or a change in rate over time. A typical endpoint for AED trials is improvement in seizure rate by greater than 50% of baseline or seizure freedom.[42] The recording of number of seizures, however, omits important information regarding the seizure qualities (intensity, duration and associated symptoms) or severity. In addition, simple counting or reporting the rate of seizures does not give information regarding seizure type and considers all seizure types as equivalent. For example, a simple partial seizure would be considered equivalent to a secondary generalized seizure despite the fact that the latter has a greater morbidity and likely a greater impact on HRQOL. Therefore, seizure severity scales have been developed to capture qualitative information that could provide an assessment of drug efficacy on seizure type.

The Engel scale was developed to compare seizure outcomes in patients who have undergone surgical resection of an epileptic focus including patients with BTRE (Table 1). The benefit of this scale is that it can be compared across surgical trials for epilepsy surgery. [43] However, the use of this scale for non-surgical brain tumor treatment trials may prove difficult in view of some of the ambiguous terminology, specifically regarding Engel class III and IV. The determination of worthwhile improvement versus no worthwhile improvement is subjective and would likely differ from physician to physician. In

2001, the ILAE proposed a new classification of seizure outcome following epilepsy surgery (Table 3). [44] The ILAE committee cited disadvantages of Engel's classification including the ambiguous terminology and the lack of a clear percentage of seizure reduction, such as greater than 50% seizure reduction, which is commonly used in epilepsy drug trials. The ILAE classification tool would clearly identify seizure-free patients as well as those with greater than 50% reduction of baseline seizures.[44]

All of the scales and studies collected clinical seizures, and did not include objective data such as EEG recordings. Therefore, some seizures can be missed. A prospective study of adult inpatients with focal epilepsy undergoing video-EEG monitoring compared patient seizure diaries to video-EEG recording.[45] A significant discrepancy in seizure reporting was seen across all seizure types but most notably in complex partial and nocturnal seizures. Patients failed to document 55.5% of all recorded seizures, 73.2% of complex partial seizures and 85.8% of nocturnal events. A left-sided EEG focus or lesion was predictive for underreporting, but no specific lobe of the brain was associated with underreporting. This study highlights some of the limitations in assessing a response to tumor treatment by using patient-reported seizure frequency; however, EEG data are not used in the assessment of a novel AED and a clinical determination of efficacy, by whatever chosen method, is the standard in epilepsy trials.

Seizure severity

Seizure frequency as a metric can provide important information if seizure severity is also assessed. Several characteristics of seizures, including duration and intensity, are useful in assessing a response to treatment. Patient or physician-reported seizure severity scales have been used to assess response of seizures to an AED. These scales include many useful data points but no scale captures all the relevant clinical data, and thus, all are imperfect.

In the Veterans Administration (VA) cooperative study, a seizure frequency and seizure severity scale was developed to be completed by a physician.[46] Although this scale allows for significant detail to be gathered regarding generalized tonic-clonic and complex partial seizures, it has proven too complex

for widespread use.[47] The Chalfont-National Hospital Scale (NHS3) was developed as a simpler version of the VA scale. This scale was also devised to be completed by the physician and by those who witnessed the seizures.[48]

The Occupational Hazard Scale evaluates seizure severity by assessing its impact on the patient's function in society.[49] The scale was used primarily to assess a patient's ability to fulfill certain occupations. The Liverpool Seizure Severity Scale is a patient reported scale.[50] The patient completes a 19-item questionnaire that is divided into two sections. The first section is perception of control and the second section includes ictal and postictal items. One potential limitation with this scale is that the patient's memory of individual seizures, specifically those associated with alteration of consciousness, may not be as accurate as a witness' recollection.[51] Although minimal difference was seen in the perception scale, this study again demonstrated that the perception scale was not as useful as the ictal scale. The Hague Seizure Severity Scale (HASS) was developed for children.[52] This was a questionnaire designed to be completed by parents only. Correlation between parent's and neurologist's scores showed comparable results but were not significant after stratification for seizure type.

A comparison of the different scales including the VA, NHS3, Occupational Hazard, Liverpool and HASS shows numerous similarities in items that are assessed (Table 4). For example, all of the severity scales assess seizure type but not in the same manner. The VA Scale assesses simple partial seizures, complex partial and generalized tonic-clonic seizures whereas the Liverpool Scale assesses all types of seizures. Surprisingly, not all scales include an assessment of seizure frequency. Seizure frequency is not a direct measure in the NHS3, Liverpool or HASS classifications. The rating scales are also arbitrary and subjective. There are no data associating specific severity scores of scales with a need to change therapy or confirming appropriate therapy. Importantly, there have not been any studies in glioma patients with epilepsy using severity scales for seizure assessment. Thus, the value of these scales in patients with LGG and BTRE is unknown.

Health-Related Quality of Life Measures and Symptom Burden.

There are several established HRQOL measures and symptom severity scales for patients with brain tumors. Commonly used tools are the European Organization for Research and Treatment of Cancer (EORTC) QLQ30 combined with the brain tumor module (BN20), the Functional Assessment of Cancer Therapy-brain (FACT-Br), the Functional Assessment of Cancer Therapy-general (FACT-G) and the M.D. Anderson Symptom Inventory – Brain Tumor (MDASI-BT).[53] These HRQOL measures have been used in large brain tumor treatment trials to assess a subjective response to brain tumor treatment. Similar patient reported outcome measures are used in AED trials.

A commonly used tool in epilepsy trials is the Quality Of Life in Epilepsy (QOLIE-31). This is a validated tool that has been used in cross cultural clinical trials assessing HRQOL as it pertains to seizure control.[54] Several of the HRQOL tools used in brain tumor treatment trials capture a limited amount of information regarding seizures. For example, the FACT-Br, BN20, and MDASI-BT include 1-2 seizure questions (Table 5). HRQOL measures in brain tumor trials have rarely focused on seizures as an independent predictor of HRQOL. For example, HRQOL measures were evaluated in 243 patients with a primary brain tumor of any grade.[55] The EORTC QLQ-30 and BN20 revealed that patients with malignant tumors and poor performance status had significantly lower HRQOL scores even before starting any adjuvant treatment. Seizures were not reported as a factor in determining HRQOL despite being present in 105 patients in this trial. A study evaluating the impact of epilepsy and AEDs in patients with primary brain tumors used neuropsychological testing and HRQOL measures.[7] One hundred fifty-six patients with epilepsy, but without clinical or radiologic signs of tumor recurrence for at least one year after histologic diagnosis, were compared to healthy controls. HRQOL was assessed by the Medical Outcome Study Short-Form Health Survey (MOS SF-36). Epilepsy burden was based on seizure frequency and AED use. In this group, 86% of patients had epilepsy and one-half of those patients using an AED were seizure-free. Patients with higher epilepsy burden manifested significant reductions in numerous cognitive domains including information processing speed, psychomotor functioning, attention functioning, verbal and working memory, executive function, and HRQOL. A higher epilepsy burden was not associated with a decrease in physical functioning (Karnofsky Performnce scale). Reductions in all

cognitive domains were attributed to the use of AEDs. Lastly, a decline in HRQOL was ascribed to the lack of complete seizure control. The use of QOLIE-31 has been shown to be more sensitive than the FACT-Br because of its focus on seizures. A study in patients with primary brain tumors and epilepsy revealed that an increased frequency of seizures was an independent risk factor for poor HRQOL when QOLIE-31 was used.[56] In patients with non-BTRE, those who reach seizure freedom reported a better HRQOL compared to those with a 90% or less reduction in seizures.[57]

Recognizing the detrimental impact of poorly controlled seizures and AED use on HRQOL in patients with idiopathic or partial epilepsy [58,59], it is likely these negative consequences would be as significant, if not more so, in patients with LGG and epilepsy. Thus, an optimal evaluation of HRQOL in patients with BTRE should include seizure-specific questions as well as questions relating to treatment with chemotherapy or RT. It is apparent that seizure-specific questions would be important in this patient population as details of this frequent symptom are limited with the current tools and more detailed information may be beneficial in future studies.

Pitfalls in the assessment of response to treatment

There are several considerations in using seizure as an outcome measure. Some of these include how to reconcile a change in seizure frequency with changes in AED dosing, especially when AED dosing is changed concurrently with tumor-directed treatment. The change in seizure frequency, whether an improvement or worsening, may be difficult to parse when multiple therapies (i.e., chemotherapy/RT) and AED adjustments are made. Also, assessing accurate seizure numbers would remain dependent on patient reporting which is subject to recall bias and recognition of all seizures. In patients with cognitive deficits from brain tumors, AED polypharmacy and chemotherapy/RT this may prove even more difficult. However, seizure counting and seizure reporting by patients or their caregivers is standard in epilepsy drug trials.

Evaluation of treatment response to an AED is based solely upon the ability to improve seizure control. Response has been defined as a 50% reduction from baseline seizure frequency. However, other

metrics are often assessed including seizure-free rates over a defined period of time. Time to first seizure, adverse effects of AED treatment, functional status and HRQOL measures are also important endpoints in AED drug trials.[60]

The timing of seizure response has not been uniform in the studies reporting seizure control after treatment with RT or chemotherapy. Follow-up timing can range from a fixed time post-treatment (ie, 6 or 12 months), or on an interval such as every 3 months. [25,33,36,61] In our opinion, assessment of seizure control should occur at all the standard clinical time points and should coincide with the immediate postoperative scan, the post-RT MRI and whenever an MRI is obtained during chemotherapy or active surveillance.

Proposed seizure assessment tool for brain tumor trials

Seizure control is unlikely to become the primary endpoint in a LGG clinical trial. However, it is an important secondary metric as seizures can be an early indicator of tumor progression, sometimes before tumor growth is evident on an MRI scan.[16] Furthermore, a change in seizure frequency is often the reason to initiate treatment, and in patients with LGG and BTRE it should be a main secondary clinical outcome measure to assess treatment response. Seizures and AEDs also need to be incorporated into HRQOL. Thus, we are proposing implementation of a new assessment tool that combines the 1989 ILAE classification system along with the ILAE outcome scale to quantify seizure control. This scale is easy to use, can be mastered by non-neurologists and has shown excellent inter-rater reliability when compared to the Engel classification. [62] Some of the benefits of this scale are that seizure free patients are separated from those with simple partial seizures defined as auras (e.g., Class 1 vs Class 2), a critical distinction when assessing treatment response. Also, it simplifies the reporting of seizures to seizure days rather than actually reporting each seizure; seizure days are defined as any calendar day in which a seizure occurs. A 50% reduction from baseline seizure day frequency is also used which mirrors the reporting of a treatment response in epilepsy drug trials. Although the original intent of this scale was to measure seizure outcomes one year after epilepsy surgery, it could be used for clinical trials in LGG patients. Using this

tool an assessment of seizure control could occur easily when every MRI is performed to assess tumor response (Fig 1).

The features of this assessment tool would include the following 4 items:

1. Seizure classification; using the modified ILAE classification.
2. Seizure frequency; using the number of seizure days from last visit.
3. Seizure outcome; using the ILAE outcome scale.
4. Seizure severity using the seizure specific questions in the existing brain tumor HRQOL or symptom burden scale.

Seizure classification in patients with LGG would be according to the ILAE classification of either a secondary generalized or focal (partial) seizure. Inclusion of subtypes such as simple motor, simple sensory, or mixed motor/sensory would be taken into consideration to distinguish those with auras (simple partial seizures of short duration only perceived by the patient) from those who are seizure-free. The ILAE scale would provide a rating system that would identify 50% improvement or worsening from baseline. As the findings could be quantified, a scale of response could be developed. For example, a complete response with regards to seizure assessment could be seizure freedom whereas a partial response would be improvement by at least one level on the ILAE scale. With regards to HRQOL, a seizure specific tool would provide comprehensive data of the effect of seizures on patients with BTRE. The QOLIE-31 would be one such tool. However, the use of seizure specific questions that exist in the established HRQOL tools currently used in glioma trials may prove more pragmatic.

We propose a pilot trial of this tool for existing brain tumor patients. In parallel, the treating physician would make an assessment of seizure burden such as whether seizure burden is better, worse, or the same from prior visit. We would then compare the objective data using the proposed tool and ILAE measures with the physician's assessment. This would allow for assessment of efficacy of this tool in capturing seizure data for patients undergoing brain tumor treatment. The pilot trial would allow for a starting point of the assessment tool and allow for modifications prior adding it to future LGG therapeutic trials. In conjunction with OS and PFS, seizure control could be used an objective outcome measure. Lastly, the

use of a HRQOL measure or symptom burden scale would enhance our assessment of seizure outcome and, in turn, treatment outcome.

References

1. Taphoorn MJ. Neurocognitive sequelae in the treatment of low-grade gliomas. *Semin Oncol*. 2003;30(6 Suppl 19): 45-48.

2. Stockhammer F, Misch M, Helms HJ, et al. IDH1/2 mutations in WHO grade II astrocytomas associated with localization and seizure as the initial symptom. *Seizure*. 2012;21(3): 194-197.

3. van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol*. 2011;12(6): 583-593.

4. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia*. 1989;30(4): 389-399.

5. Cascino GD. Epilepsy and brain tumors: implications for treatment. *Epilepsia*. 1990;31 Suppl 3: S37-44.

6. Mittal S, Barkmeier D, Hua J, et al. Intracranial EEG analysis in tumor-related epilepsy: Evidence of distant epileptic abnormalities. *Clin Neurophysiol*. 2016;127(1): 238-244.

7. Klein M, Engelberts NH, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life. *Ann Neurol*. 2003;54(4): 514-520.

8. Maschio M, Sperati F, Dinapoli L, et al. Weight of epilepsy in brain tumor patients. *J Neurooncol*. 2014;118(2): 385-393.

9. Klein M, Heimans JJ, Aaronson NK, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. *Lancet*. 2002;360(9343): 1361-1368.

10. Koekkoek JA, Kerkhof M, Dirven L, Heimans JJ, Reijneveld JC, Taphoorn MJ. Seizure outcome after radiotherapy and chemotherapy in low-grade glioma patients: a systematic review. *Neuro Oncol*. 2015;17(7): 924-934.

11. Gilliam F, Kuzniecky R, Faught E, Black L, Carpenter G, Schrodt R. Patient-validated content of epilepsy-specific quality-of-life measurement. *Epilepsia*. 1997;38(2): 233-236.

12. Isojarvi JI. Reproductive dysfunction in women with epilepsy. *Neurology*. 2003;61(Suppl): S27-34.

13. Isojarvi JI, Lofgren E, Juntunen KS, et al. Effect of epilepsy and antiepileptic drugs on male reproductive health. *Neurology*. 2004;62(2): 247-253.

14. Nevalainen O, Ansakorpi H, Simola M, et al. Epilepsy-related clinical characteristics and mortality: a systematic review and meta-analysis. *Neurology*. 2014;83(21): 1968-1977.

15. Smithson WH, Colwell B, Hanna J. Sudden unexpected death in epilepsy: addressing the challenges. *Curr Neurol Neurosci Rep*. 2014;14(12): 502.

16. Koekkoek JA, Dirven L, Heimans JJ, et al. Seizure reduction is a prognostic marker in low-grade glioma patients treated with temozolomide. *J Neurooncol*. 2015;126(2)347-354.

17. You G, Sha ZY, Yan W, et al. Seizure characteristics and outcomes in 508 Chinese adult patients undergoing primary resection of low-grade gliomas: a clinicopathological study. *Neuro Oncol*. 2012;14(2): 230-241.

18. Krueger DA, Wilfong AA, Holland-Bouley K, et al. Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. *Ann Neurol*. 2013;74(5): 679-687.

19. Ruda R, Soffietti R. What is New in the Management of Epilepsy in Gliomas? *Curr Treat Options Neurol*. 2015;17(6): 351.

20. Chang EF, Potts MB, Keles GE, et al. Seizure characteristics and control following resection in 332 patients with low-grade gliomas. *J Neurosurg*. 2008;108(2): 227-235.

21. Englot DJ, Berger MS, Barbaro NM, Chang EF. Predictors of seizure freedom after resection of supratentorial low-grade gliomas. A review. *J Neurosurg*. 2011;115(2): 240-244.

22. Sugano H, Shimizu H, Sunaga S. Efficacy of intraoperative electrocorticography for assessing seizure outcomes in intractable epilepsy patients with temporal-lobe-mass lesions. *Seizure*. 2007;16(2): 120-127.

23. Chan CH, Bittar RG, Davis GA, Kalnins RM, Fabinyi GC. Long-term seizure outcome following surgery for dysembryoplastic neuroepithelial tumor. *J Neurosurg*. 2006;104(1): 62-69.

24. van den Bent MJ, Afra D, de Witte O, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet*. 2005;366(9490): 985-990.

25. Ruda R, Magliola U, Bertero L, et al. Seizure control following radiotherapy in patients with diffuse gliomas: a retrospective study. *Neuro Oncol*. 2013;15(12): 1739-1749.

26. Rossi GF, Scerrati M, Roselli R. Epileptogenic cerebral low-grade tumors: effect of interstitial stereotactic irradiation on seizures. *Appl Neurophysiol*. 1985;48(1-6): 127-132.

27. Rogers LR, Morris HH, Lupica K. Effect of cranial irradiation on seizure frequency in adults with low-grade astrocytoma and medically intractable epilepsy. *Neurology*. 1993;43(8): 1599-1601.

28. Schrottner O, Unger F, Eder HG, Feichtinger M, Pendl G. Gamma-Knife radiosurgery of mesiotemporal tumour epilepsy observations and long-term results. *Acta Neurochir Suppl*. 2002;84: 49-55.

29. Shankar A, Rajshekhar V. Radiological and clinical outcome following stereotactic biopsy and radiotherapy for low-grade insular astrocytomas. *Neurol India*. 2003;51(4): 503-506.

30. Plathow C, Schulz-Ertner D, Thilman C, et al. Fractionated stereotactic radiotherapy in low-grade astrocytomas: long-term outcome and prognostic factors. *Int J Radiat Oncol Biol Phys*. 2003;57(4): 996-1003.

31. Mason WP, Krol GS, DeAngelis LM. Low-grade oligodendroglioma responds to chemotherapy. *Neurology*. 1996;46(1): 203-207.

32. Brada M, Viviers L, Abson C, et al. Phase II study of primary temozolomide chemotherapy in patients with WHO grade II gliomas. *Ann Oncol*. 2003;14(12): 1715-1721.

33. Pace A, Vidiri A, Galie E, et al. Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response. *Ann Oncol*. 2003;14(12): 1722-1726.

34. Soffietti R, Ruda R, Bradac GB, Schiffer D. PCV chemotherapy for recurrent oligodendrogliomas and oligoastrocytomas. *Neurosurgery*. 1998;43(5): 1066-1073.

35. Sherman JH, Moldovan K, Yeoh HK, et al. Impact of temozolomide chemotherapy on seizure frequency in patients with low-grade gliomas. *J Neurosurg*. 2011;114(6): 1617-1621.

36. Koekkoek JA, Dirven L, Heimans JJ, et al. Seizure reduction in a low-grade glioma: more than a beneficial side effect of temozolomide. *J Neurol Neurosurg Psychiatry*. 2015;86(4): 366-373.

37. Blonski M, Taillandier L, Herbet G, et al. Combination of neoadjuvant chemotherapy followed by surgical resection as a new strategy for WHO grade II gliomas: a study of cognitive status and quality of life. *J Neurooncol*. 2012;106(2): 353-366.

38. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*. 2010;51(4): 676-685.

39. Grinnon ST, Miller K, Marler JR, et al. National Institute of Neurological Disorders and Stroke Common Data Element Project - approach and methods. *Clin Trials*. 2012;9(3): 322-329.

40. Glueckauf RL, Girvin JP, Braun JR, Bochen JL. Consistency of seizure frequency estimates across time, methods, and observers. *Health Psychol*. 1990;9(4): 427-434.

41. Neugebauer R. Reliability of seizure diaries in adult epileptic patients. *Neuroepidemiology*. 1989;8(5): 228-233.

42. Cramer JA. Alternate endpoints for seizure measurement. *Adv Neurol*. 1998;76: 189-194.

43. Engel J. Jr. VNPC, Rasmussen T.B., et. al. Outcome with Respect to Epileptic Seizures. In: Jr EJ, ed. *Surgical Treatment of the Epilepsies*. New York: Raven Press; 1993:609-621.

44. Wieser HG, Blume WT, Fish D, et al. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia*. 2001;42(2): 282-286.

45. Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. *Arch Neurol*. 2007;64(11): 1595-1599.

46. Cramer JA, Smith DB, Mattson RH, Delgado Escueta AV, Collins JF. A method of quantification for the evaluation of antiepileptic drug therapy. *Neurology*. 1983;33(Suppl): 26-37.

47. Cramer JA, French J. Quantitative assessment of seizure severity for clinical trials: a review of approaches to seizure components. *Epilepsia*. 2001;42(1): 119-129.

48. O'Donoghue MF, Duncan JS, Sander JW. The National Hospital Seizure Severity Scale: a further development of the Chalfont Seizure Severity Scale. *Epilepsia*. 1996;37(6): 563-571.

49. Janz D. How does one assess the severity of epilepsy? . In: Trimble MR, ed. *Chronic epilepsy: Its prognosis and management.* New York: John Wiley; 1989:21-53.

50. Baker GA, Smith DF, Dewey M, Morrow J, Crawford PM, Chadwick DW. The development of a seizure severity scale as an outcome measure in epilepsy. *Epilepsy Res*. 1991;8(3): 245-251.

51. Rapp S, Shumaker S, Smith T, Gibson P, Berzon R, Hoffman R. Adaptation and evaluation of the Liverpool Seizure Severity Scale and Liverpool Quality of Life battery for American epilepsy patients. *Qual Life Res*. 1998;7(6): 467-477.

52. Carpay JA, Vermuelen J, Stroink H, et al. Seizure severity in children with epilepsy: a parent-completed scale compared with clinical data. *Epilepsia*. 1997;38(3): 346-352.

53. Armstrong TS, Gilbert MR. Patient reported endpoints for measuring clinical benefit in (high grade glioma) primary brain tumor patients. *Curr Treat Options Oncol*. 2014;15(4): 519-528.

54. Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. *Epilepsia*. 1998;39(1): 81-88.

55. Budrukkar A, Jalali R, Dutta D, et al. Prospective assessment of quality of life in adult patients with primary brain tumors in routine neurooncology practice. *J Neurooncol*. 2009;95(3): 413-419.

56. Rahman Z, Wong CH, Dexter M, et al. Epilepsy in patients with primary brain tumors: The impact on mood, cognition, and HRQOL. *Epilepsy Behav*. 2015;48: 88-95.

57. McLachlan RS, Rose KJ, Derry PA, Bonnar C, Blume WT, Girvin JP. Health-related quality of life and seizure control in temporal lobe epilepsy. *Ann Neurol*. 1997;41(4): 482-489.

58. Lee SA, Kim MJ, Lee HW, et al. The effect of recurrent seizures on cognitive, behavioral, and quality-of-life outcomes after 12months of monotherapy in adults with newly diagnosed or previously untreated partial epilepsy. *Epilepsy Behav*. 2015;53: 202-208.

59. Kobau R, Cui W, Kadima N, et al. Tracking psychosocial health in adults with epilepsy--estimates from the 2010 National Health Interview Survey. *Epilepsy Behav*. 2014;41: 66-73.

60. Ben-Menachem E, Sander JW, Privitera M, Gilliam F. Measuring outcomes of treatment with antiepileptic drugs in clinical trials. *Epilepsy Behav*. 2010;18(1-2): 24-30.

61. Warnke PC, Berlis A, Weyerbrock A, Ostertag CB. Significant reduction of seizure incidence and increase of benzodiazepine receptor density after interstitial radiosurgery in low-grade gliomas. *Acta Neurochir Suppl*. 1997;68: 90-92.

62. Durnford AJ, Rodgers W, Kirkham FJ, et al. Very good inter-rater reliability of Engel and ILAE epilepsy surgery outcome classifications in a series of 76 patients. *Seizure*. 2011;20(10): 809-812.

Figure Legend:

Figure 1. Proposed Seizure Assessment Tool